

# Estimating Avoidable Causes of Cancer

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Evidence that much cancer is preventable derives from observations of time trends and geographic patterns of cancer, birth cohort changes, high risks in groups with well-defined exposures, and experimental studies. In an effort to identify additional opportunities for reducing the impact of cancer on society, this conference assessed avoidable causes of cancer. The magnitude and extent of preventable causes of cancer are subjects of intense debate, with discrepancies often related to the use of different time frames and different weights for epidemiologic and toxicologic evidence. There is much agreement, however, about the exposures that increase risk, notably tobacco, alcohol, diet, radiation, medications, occupational exposures, general environmental exposures, and infectious agents. Interactions between carcinogenic exposures and genetic susceptibility are also important. Concerted efforts are needed to identify avoidable causes of cancer and to apply knowledge already obtained to reduce the cancer burden. — *Environ Health Perspect* 103(Suppl 8):301–306 (1995)

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## Estimating Avoidable Causes of Cancer

Twenty-two years and \$30 billion after the formal launching of the Federal war on cancer, age-adjusted rates of new cases of cancer continue to increase (1). Tobacco smoking remains the single most important preventable cause of cancer and other diseases in the developed world (2). While smoking and improved technology account for much of the increase, some unexplained patterns of cancer persist (1,3,4).

The political impetus for a nationwide national cancer program arose because cancer was believed by many to be treatable with medicines and other interventions that would produce results similar to those achieved when antibiotics significantly reduced previously fatal infectious diseases. The central focus of the early war on cancer was, thus, on devising new methods of earlier treatment and diagnosis of this group of diseases. At the outset of the national cancer effort, little emphasis was placed on seeking ways to postpone, avoid, or prevent some portion of cancer.

Evidence that much cancer is, in principle, preventable derives from three different sets of observations (5). First, time trends and geographic patterns of cancer reveal that even among developed countries rates of deaths and new cases of cancer vary substantially (6,7), relatively younger birth cohorts in several countries are experiencing higher rates of cancer incidence than are estimated to have occurred in older birth cohorts (1,8) and rates of new cases, in addition to those linked to smoking, have increased in many developed countries (1,3,6–9). Second, some groups with unusually well-defined exposures such as cigarette smokers (10), blue-collar workers (11), and farmers (12) have higher rates of certain forms of cancer than persons without such exposures. Finally, experimental studies have identified a number of compounds to which general population exposures can be common that significantly increase cancer in animals or in experimental cell cultures.

In an effort to identify additional opportunities for reducing the impact of cancer on society, this conference assessed avoidable causes of cancer, drawing on all three types of evidence described above. For purposes of discussion, an avoidable cause of cancer is any exposure or contributing factor that increases the risk of cancer and is amenable to social or personal interventions that can ultimately keep people from developing the disease. Preventable causes of cancer include any contributing factor such as age of first childbirth and number of children, and sexual promiscuity that social programs may not easily alter or that are implausible or inappropriate. Many of the known

causes of cancer such as reproductive behavior and family history, faulty diet, smoking and drinking and other addictive habits, while theoretically preventable, are either immutable or highly resistant to change. Moreover, longstanding host factors, such as common occupation, place of residence, use of alcohol, and general nutritional status can shift over time; these factors can greatly affect susceptibility to other external cancer-causing agents.

Many researchers have estimated that environmental factors, broadly conceived, account for about 75 to 80% of all cancer in developed countries. In principle, many of these could be avoided by strategies that reduce key exposures and other risk factors. Any estimate of the proportion of all cancer that is avoidable assumes that rates of cancer in the lowest risk countries for which reasonable quality data exist provide baseline indications of the spontaneous or background levels of disease. These baselines can be contrasted with those that occur in the highest risk countries.

## Measurement of Preventable Cancer

The magnitude and extent of preventable causes of cancer have been subjects of intense debate. Any such estimates involve complex and multiple assumptions and draw inferences from often incomplete sources of information. Two distinct time frames can be applied to the identification and assessment of avoidable cancer causes, and the use of these different time frames accounts for most of past disagreements on the subject.

One time frame begins with current human patterns of cancer and attempts to ascertain how much of what has occurred

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Abbreviations used: ECU, European Community Unit; EMF, electromagnetic field; IARC, International Agency for Research on Cancer.

in the past and is occurring today can be explained by known risk factors. Current variations in cancer patterns reflect historical factors including cigarette smoking, diet, alcohol, behavior, workplace and environmental exposures, drugs, medical and family history. Patterns that cannot be explained in terms of these known risk factors are then presumed to be due to other factors that need to be identified.

Another method begins with estimated exposures to known or suspected risk factors (identified in both human and animal studies) and attempts to determine the projected impact of these estimated current exposures on future cancer patterns.

The latter approach involves a greater reliance on experimental evidence of laboratory studies in whole animals and cell cultures and makes estimates of exposure to these materials in the human population, whereas the former approach rests on the less debatable subject of human death registries and case reports of cancer.

A decade ago much of the discrepancy between earlier estimates of avoidable causes were related to the use of different time frames and decidedly different weights for epidemiologic and toxicologic evidence. Doll and Peto (13) analyzed past human patterns of disease from 1933 to 1977, whereas Bridbord et al. (14) predicted future patterns of disease based on estimated exposures to known and suspected hazards. Each represents a valid analytic approach.

This paper relies on both human epidemiologic and experimental evidence and exposure estimates, which were presented to the President's Cancer Panel on Avoidable Causes of Cancer, to lay the foundation for a new effort to achieve consensus on this matter. Almost 15 years have elapsed since the last major efforts were made to assess avoidable causes of cancer, and many more relevant studies now exist.

### Tobacco

There is universal agreement that tobacco is a preventable cause of cancer. It causes not only lung cancer but also cancer of the bladder, mouth, esophagus, pharynx, larynx, and cervix uteri (15). Tobacco is responsible for roughly one in five deaths in the United States, and about one in three cancer deaths in men.

Prevention works: reductions in lung cancer in white males in the United States and in the United Kingdom bear witness to the effect of reductions in smoking. But smoking-related cancer continues to rise

among women, among African-Americans, and in most developing countries. Given the important role of smoking in public health, wider programs for nicotine addiction treatment should be encouraged and evaluated, and tobacco subsidies, advertising, and tax policies must be rethought (16).

This conference did not address the question of the political will to intervene, which poses a universal dilemma. The European Community allots about 8 million ECU (its new currency) per year to its cancer program but gives 1200 million ECU to the support of tobacco farmers. In countries that have tried them, tax increases seem to work, but they must be regionally applied or they tend to foster bootlegging and black markets. Also, the ban on advertising seems to work, as does antismoking advertising, but these approaches are under constant attack from tobacco proponents.

The United States is particularly fortunate in that there is now substantial public opinion against smoking. Despite this climate, the annual advertising budget for tobacco in the United States is more than twice the annual budget for the National Cancer Institute. The pressure of public opinion against smoking unfortunately does not exist in all countries. The increase in smoking in developing countries, especially in women, is especially worrisome and constitutes a serious public health problem for the next century.

### Alcohol

One paper presented at this conference spawned an interesting debate on the balance between the beneficial and the deleterious effects of alcohol (17). It must be recognized that excessive consumption leads to a wide spectrum of harmful consequences (18). In relation to cancer, the smoking-alcohol interaction is often categorized by a multiplicative dose response. The incidence of many cancers of the head and neck and of the esophagus could be substantially lowered if there were reductions in alcohol and smoking.

The question of a possible link between alcohol and cancer of the breast was discussed. The relative risks appear to be low, but the attributable risks could be considerable for this common tumor. The role of alcohol in the development of breast cancer needs to be explored further: women should be informed and additional studies must be undertaken on this association and on whether there could be a threshold for the effect.

### Diet

Everybody eats. We have amassed a wealth of information on the way diet influences cancer risk (19), although assessing past dietary exposures remains our Achilles' heel, as Lenore Kohlmeier aptly reminded us (20). In our opinion, the most rational interpretation of all the epidemiological evidence, including that from changes in cancer risk in migrants, is that around 30% of cancer is in some way conditioned by diet. Whether and to what extent dietary factors can be modified by social policy should be subject of considerable research and intervention studies (21).

The possible roles of fat (both per se and as a vehicle for contaminants), red meat, fruits, vegetables, folates, calcium, height, weight, exercise, and other factors need to be carefully assessed. Until the underlying mechanisms can be described more precisely, effective intervention cannot be guaranteed. In addition, more research is needed on the anticarcinogens in food, as well as the potential roles of natural and synthetic xenoestrogens.

We need to improve methods for measuring many aspects of diet and to develop biologic markers of past dietary habits. Case-control studies may not be the best way to study diet, given that the results frequently are not reproducible in cohort investigations.

The possible importance of diet in childhood was briefly mentioned at this conference. Research on cardiovascular disease by Barker and colleagues in England (22-25) and on breast cancer among populations who have migrated to the United States (26-28) suggests a major influence of diet in childhood. The need to retrospectively assess diet in childhood may make dietary research even more difficult than it is now.

If some constituents of red meat really do increase cancer risk, there will have to be a revolution in agricultural practice. In this case, the populations in developing countries may benefit by retaining current dietary patterns rather than seeking to adopt more Occidental dietary lifestyles.

A high-energy intake may not be advantageous. The advantages of routine exercise are becoming apparent, notably for colon and breast cancer, with those who engage in vigorous, regular exercise earlier in life showing the greatest benefit.

One of the enigmas in the United States has been the extraordinary rapidity of the rise in the levels of large bowel cancer in the Japanese migrant population (29).

The Japanese are but one of the many recent migrant populations in the United States. Some migrants to the United States came over in the Mayflower; others have come more recently across the Mexican border. If one could study the diets of recent migrants before they become Americanized, much could probably be learned. Long-term study is needed, and this requires long-term funding.

In our opinion, this very difficult area requires a major investment in research effort. Diet-related cancer can never be eliminated, but it should be possible in time to reduce the risk burden by devising sound agricultural and educational policies based on current knowledge and ensuring that additional information is acquired.

### General Environment

The role of the general environment in cancer causation was actively reviewed and discussed (30–32). There was consensus that polluted atmosphere and polluted water are to be avoided if only because of undesirable aesthetic aspects. Further, it was agreed that studying the effects of environmental pollution remains one of the most challenging and frustrating parts of epidemiologic research and involves large numbers of people whose exposures change over time and are often poorly characterized. Still, while the relative risk of environmental pollution surely is small, the attributable risk remains potentially large, since all people breathe air, drink and bathe in water, and eat food. In part, given the limited human data, past assessments were based on experimental animal studies of highly controlled exposures to individual compounds. This has the advantage of specificity and the disadvantage that humans are never exposed so neatly but rather must contend with a multitude of low levels of common pollutants. Assessing their overall impact will require astute and innovative work with geographic information systems and other methods to refine the estimate of exposures (32,33).

Some evidence was presented that cleaner air and water could prevent about 10% of cancers of the lung (especially in nonsmokers), and between 20 to 40% of cancers of the bladder and possibly the rectum (30,31). Populations exposed to agents that are also common on farms, such as household lawn and garden chemicals, may also incur risks, but these are not yet quantified. General environmental exposures remain an important and challenging area for research, especially in light of public interest and concern about these matters.

### Hormones and Medication

People are usually exposed to drugs for short periods making assessment of their long-term consequences difficult. However, some drugs are taken for prolonged periods, drugs such as oral contraceptives and medications for peptic ulcer, allergies, depression and other psychological problems, and epilepsy. There is general agreement that drugs should be avoided by women immediately before and during pregnancy and lactation, and by men for 4 months before they try to become fathers.

The benefits and disadvantages of hormone replacement therapy and the use of oral contraception are under serious review (34). Oral contraceptives reduce the risk of endometrial and ovarian cancer (and perhaps osteoporosis and heart disease), but possibly increase the risk of other cancers, notably breast. It is important to differentiate the relative risk that occurs with different doses, formulations, and ages of first use.

In addition to hormones, many of the drugs used in cancer chemotherapy have been linked with increasing the risk of second primary tumors (35). The carcinogenic activity of the antineoplastic drugs mandates long-term monitoring of the fate of cancer patients, which necessitates quality cancer registries. Patients treated with immunosuppressive drugs also need long-term follow-up. If tamoxifen becomes generally available as a prophylactic rather than a therapeutic agent, those taking this agent also will need to be followed carefully to determine whether they have excesses of liver, stomach, and colon cancer, as some have reported.

### Occupation

Despite the heated debate about the likely number of U.S. cancer deaths that are or will be attributable to occupation, no routine system has been adopted in the United States to generate reliable information. Regrettably we must reiterate the analysis of Doll and Peto from 1981: "On present knowledge, therefore, it is impossible to make any precise estimate of the proportion of the cancers today that are attributable to hazards at work... It is therefore, odd that despite the passionate debates that have taken place about the likely magnitude of the number of U.S. cancer deaths that are or will be attributable to occupation, no routine system has been adopted in the U.S. for generating reliable information" (13). Small studies of exposed workplaces frequently do not have sufficient statistical power and are not substitutes for systematic

worker surveillance and monitoring, which could provide early warnings and clarify the nature of relative risks involved.

The risk due to a single agent and that due to complex exposures associated with, for example, being a painter, were considered (11). The exposures underlying the higher rates of some cancers in farmers need to be ascertained (36) and better regulated (37). Studies of farmers may offer some interesting clues about avoidable causes of cancer in the general population, given that the same tumors that occur more frequently in farmers are also increasing in developed countries.

There has been much discussion and some confusion about the relative importance of occupation as a cause of cancer (38). Blue-collar employment in the United States has continued to decline as a percent of total employment since the 1950s. Accordingly, exposures to industrial workplace hazards can be expected to play less of a role for future overall cancer rates, i.e., the attributable risk from blue-collar workplace exposures will surely be less in the future than in the past. But the relative risk for some highly exposed workers may remain high. Overall, however, work exposures appear to account for less than 8% of all cancers in males and fewer in females.

The attitudes of industry were not discussed but are of obvious importance. If the asbestos industry had acted sooner, numerous deaths from mesothelioma and lung cancer would have been avoided. Avoidance of occupational cancer is in the hands of both industry, through the provision of a safe working environment, and the work force by adherence to safety rules.

Evidence that workplace exposures do not stay within neat boundaries comes from recent reports that up to one-third of recent mesothelioma cases have no known occupational history of exposure to asbestos (39). Long believed to be uniquely associated with asbestos exposure, these mesothelioma cases pose important enigmas for public health. We must attempt to determine how exposures have occurred in these cases and whether some other agents could be involved.

### Radiation

The public fears ionizing radiation, which is responsible for less than 2% of cancer deaths (40,41). There is concern about all types of radiation and about the interaction of one form, radon, and smoking. Based on current evidence, it appears prudent to reduce radon exposure in the home.

Nuclear accidents and the disposal of nuclear wastes present other problems, as the public has been vividly reminded since Chernobyl. Diagnostic medical exposures seem by and large to be involving doses that are hundreds, if not thousands, of times lower than four decades ago. Routine mammographic screening can save lives in women over 50 years of age. However, such screening for breast cancer in very young women and in those with a family history of breast cancer might increase their risk (42). Recent concerns have been expressed about exposures from uncontrolled medical waste incineration, which can include low levels of radionuclides along with organochlorines and metals.

Light spans a continuum of wavelengths from visible to invisible, with varying biologic properties. Ultraviolet light produces distinct changes in skin epithelium, which have been linked to unique genetic changes and can cause malignant melanoma and nonmelanoma skin cancer, including squamous cell and basal cell carcinoma (43). The sun remains the single most important source of exposure to ultraviolet rays, and care with regard to exposure is recommended. A major portion of all skin cancer appears to be avoidable by a combination of personal behavior and social policy (44). Using protective clothing and possibly sunscreens can reduce sunburn, as can avoiding tanning parlors and the more dangerous peak solar exposures.

Social policies should be devised that discourage outdoor activities at peak sun exposure times in the summer, restrict the use of ozone-depleting chemicals, and preserve the stratospheric ozone layer, which filters incoming ultraviolet rays.

### Electromagnetic Fields

Considerable debate surrounds the matter of how best to measure and assess lifetime exposures to electromagnetic fields (EMF) (45). Occupational cohort studies have detected excesses of some unusual cancers, such as leukemia, male breast, and brain. Studies of household EMF exposure have been inconsistent, perhaps reflecting the different measures applied to EMF. Some studies have assessed EMF in terms of electrical fields, others have incorporated measures of radio frequency, and still others rely on wiring code, or distance lived from high voltage power lines and transformers. We will have to see what emerges from current and future studies. It is possible that most of the recorded risk to date may ultimately be linked to other confounding

exposures, although that seems less likely as more studies with similar results accumulate from different countries. If there is a risk, remedial action could well be expensive.

### Infective and Parasitic Agents

In the developing world, infective and parasitic agents are major causes of most common forms of cancer (46–48). Development of cost-effective vaccines to prevent infection could radically alter this picture and will require public health commitment and vigilance. Although there is an effective, cheap vaccine for hepatitis-B, it will take at least 25 years before the Gambian study coordinated by the International Agency for Research on Cancer (IARC) demonstrates whether neonatal vaccination reduces the risk of developing primary liver cancer in adults. The importance of this trial cannot be overstated, as in many parts of the developing world, this is a leading form of cancer.

A vaccine for the Epstein-Barr virus may protect against Burkitt's lymphoma, nasopharyngeal carcinoma, and perhaps some Hodgkin's disease, as well as infectious mononucleosis, but evaluation will not be easy. Should a vaccine be developed for the strains of human papilloma virus (HPV) associated with the second most common female cancer in the world today, i.e., cervix uteri, the following questions would need to be answered. At what age should the vaccine be given? To whom should it be given? How would its effectiveness be evaluated?

Are there viruses as yet undiscovered that give rise to cancer? What is the relative and attributable risk of *Helicobacter pylori* to gastric cancer, IARC has just classified the organism as a human carcinogen, yet not everyone exposed acquires the disease. Are other bacteria involved in other neoplasms? Do they function as promoters or work through nutritional co-factors?

The cancers associated with bilharzia, clonorchis, and opisthorchis are preventable today if the cycle of infection can be broken by sound hygiene practices and interventions, which fall within the realm of public health measures. Avoidance of the HPV infections linked with cervix uteri cancer requires changes in social structures and sexual mores. It is possible that reduction of deprivation may influence the frequency and effect of *H. pylori* infection.

### Genetic Susceptibility

Scientists have achieved a number of impressive discoveries regarding the role of

genes in the development of cancer (49,50). Inherited loss of function of cancer-causing genes appears to lead to development of breast cancer in 10% or fewer of all cases. Can we avoid our genes? It is not likely. Can we mend our defective genes? Some suggestions were made that this may be possible eventually, although it is unlikely to be achieved in the near future.

However, the signal question today is: Who should have access to the information about genetically mediated susceptibility, which is becoming available? At a recent meeting in Britain on setting the national cancer agenda (C Muir, personal communication), two priorities emerged: one, action on tobacco; two, ground rules for who should have access to the information about the susceptibility an individual may be found to have.

### Deprivation

Both Samuel Broder and Harold Freeman stated (oral communications) that poverty is a carcinogen. Poverty can be equated in many circumstances with a lack of education. The two seem to go hand in hand, regardless of the culture being considered. But this is not entirely a one-way process. It is not always advantageous to be rich.

Data from Scotland presenting the incidence, age adjusted to the European Standard Population, of lung cancer by quintile of deprivation category can be analyzed. For males there is a very substantial difference, with the age-standardized rates being almost 2-fold greater among the deprived. The same holds true for females. But for malignant melanoma, the gradient goes in the opposite direction and is particularly noticeable in females.

For the much more common breast cancer, the relatively prosperous have an age-standardized incidence rate of 105 per 100,000, whereas among the most deprived the rate is just under 80. Hence, poverty or deprivation—and deprivation goes far beyond base income—operates in both directions in terms of cancer risk.

The interaction of ethnicity and deprivation was mentioned. There is some evidence that there may be genetic differences in the metabolizing enzymes according to ethnic group, which may explain some of the risk differentials.

### Precautionary Principle

The precautionary principle holds that we should take care not to engage in activities that appear likely to increase widespread risks, even though we are uncertain about

the size and extent of those risks. Public policy should not err too far in the wrong direction. Originally generated in discussions of global well being, this principle can be extended to the public health arena. The puzzling growth in new cases of cancer not linked to smoking and in health care costs has fostered a renewed search for factors, in addition to smoking, workplace hazards, and alcohol, that could postpone the onset or avoid altogether the occurrence of some fraction of cancer. Opportunities for additional preventive strategies need to be extracted from current patterns of the disease.

Lessons related to the decline in infectious disease in the nineteenth century offer some grounds for optimism about the beneficial impacts of precautionary actions. During that epoch, fundamental advances in sanitation, housing, nutrition, and working conditions, led to major reductions in infectious diseases. Improvements in public life arose not out of specific scientific hypotheses but from shared sentiments about social welfare and other vague concepts. Real declines in infectious deaths occurred long before the germ theory of disease had been advanced, specific viruses and bacteria identified, and remedies devised to neutralize their deadly effects. Thus, within a decade of crude filters being required on public water supplies in London, rates of deaths from cholera subsided markedly. This drop in fatal disease was achieved long before the cholera vibrio had been theorized and seen under the microscope.

Today, it is possible that basic improvements in how and what we eat, what drugs we take, whether we exercise recreationally, and in our chemical-physical environment, such as recycling and reduced toxic emissions, might also benefit public health, even though the cellular and genetic mechanisms of cancer are not fully understood. Multiple exposures to combinations of low levels of common pollutants and other cancer-causing factors could well be explanations for part of the persisting patterns of cancer that are otherwise inexplicable.

### Policy Dilemmas

Even where specific cancer-causing materials have been clearly identified, developing and implementing social policies to reduce exposures and avoid cancer present some bewildering social challenges. Consider how long modern societies debated whether to take any decisive actions to discourage cigarette smoking. While

polemics about the relative role of cigarette smoking raged over the past 50 years, millions became hooked by this potent cause of cancer. In the meantime, a complex set of agricultural subsidies evolved to support the production of tobacco in most southern state economies. In this regard, the struggles over tobacco control provide an unfortunate paradigm that is relevant to any attempt to reduce exposures to known or suspected cancer-causing materials, which are also key materials in commerce.

### Opportunities for Prevention

A growing body of experimental and human evidence has identified other risk factors for cancer in addition to smoking. Because cancer is a disease with multiple causes, many of which are not susceptible to human intervention, any single contributing factor usually accounts for only a proportion of all cases. Still, efforts to identify these avoidable causes are a vital part of public health strategies to reduce the disease burden and promote health. In assessing the relative contribution of various factors to health, epidemiologists are constrained by the fact that the real world is elaborate and chaotic. Laboratory studies provide controlled scientific studies of suspect agents and their health consequences, but in the real world people encounter multiple agents at inconstant intervals. Because diseases have multiple and sometimes competing causes, knowledge about the relative magnitudes and extent of contributing causes will always be incomplete.

While the combined avoidable causes of cancer from diet, exercise, alcohol and smoking are estimated to account for about 70% of all cancers, in fact, these causes do not neatly account for this proportion of all cancer. Avoidable causes are not necessarily additive, as they function in a contributory manner. Thus, they may be thought of as necessary but not sufficient causes in the customary logical framework. Moreover, intriguing interactions are likely to occur. Thus, diet involves not only the active constituents of food products, such as the beneficial components of omega 3 fatty acids in olive oil, but also potentially harmful contaminants such as lipophilic organochlorine residues in animal fat.

There is no denying that it has proven difficult for political will to coalesce around preventive strategies for a variety of reasons that reflect the struggles of postmodern democratic societies to achieve sustainable development. Despite these difficulties, or perhaps because of them, scientists have a

special obligation to pursue opportunities to prevent cancer and to present their information in ways that can be understood by those who are not experts in the field. At its core, cancer prevention is not a political issue but a matter of public health and common sense. Human capital is strengthened by policies that promote health and reduce disease.

No matter how efficient we may become at delivering health care, we must also seek to reduce demand by keeping people from developing diseases in the first place. Recent analyses of cancer patterns summarized here and reported widely elsewhere indicate that we need to make a concerted effort to identify avoidable causes of cancer in addition to smoking, and to apply knowledge already obtained about dietary, workplace, and other hazards to reducing the present cancer burden. If we were to prevent only one-fourth of all cancers each year, we would spare more than a quarter million people and their families from this often disfiguring and disabling disease, and spare society of the burgeoning financial and human costs.

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